(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 958 821 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
24.11.1999 Bulletin 1999/47

(21) Application number: **97934737.4**

(22) Date of filing: **07.08.1997**

(51) Int. Cl.[6]: **A61K 31/52**, A61K 9/107, C07D 473/08

(86) International application number:
PCT/JP97/02773

(87) International publication number:
WO 98/05334 (12.02.1998 Gazette 1998/06)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
RO SI

(30) Priority: **07.08.1996 JP 22439996**

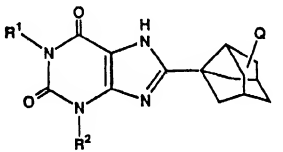
(71) Applicant:
KYOWA HAKKO KOGYO CO., Ltd.
Chiyoda-ku, Tokyo 100 (JP)

(72) Inventors:
- **HOSOKAWA, Toshihito**
  Sunto-gun, Shizuoka-ken 411 (JP)
- **IWATA, Kenji**
  Sunto-gun, Shizuoka-ken 411 (JP)
- **KAWAGUCHI, Yuji**
  Sunto-gun, Shizuoka-ken 411 (JP)
- **KATO, Yasuki**
  Sunto-gun, Shizuoka-ken 411 (JP)
- **ITO, Kunio**
  Sunto-gun, Shizuoka-ken 411 (JP)

(74) Representative:
VOSSIUS & PARTNER
Siebertstrasse 4
81675 München (DE)

(54) **FAT EMULSION CONTAINING XANTHINE DERIVATIVE**

(57)



(I)

A fat emulsion comprising a xanthine derivative represented by general formula (I) or a pharmacologically acceptable salt thereof, wherein R^1 and R^2 represent each independently substituted or unsubstituted lower alkyl, and Q represents hydrogen, hydroxyl or substituted hydroxyl.

EP 0 958 821 A1

Description

Technical Field

[0001] The present invention relates to a fat emulsion containing a xanthine derivative or a pharmacologically acceptable salt thereof, which exhibits an adenosine A1 receptor antagonizing activity, and which has antihypertensive activity, diuretic activity, kidney-protecting activity, bronchiodilatary activity, brain function-improving activity and antidemential activity.

Technical Background

[0002] Renal insufficiency, especially, acute renal insufficiency is such a serious disease that waste materials are accumulated in the blood owing to the deficiency of the renal function, and the development of an agent for preventing, curing or treating the renal insufficiency has been in demand. It is required to elucidate the renal function and to develope an appropriate treatment of the renal functional insufficiency.

[0003] It has been long known that xanthines such as caffeine, theophylline and the like possess diuretic activity. In recent years, studies have been made with respect to the diuretic activity of these xanthines, and it has been clarified that the xanthines act as an antagonist of an adenosine receptor. Further, in recent years, it has been discovered that 8-(3-noradamantyl)-1,3-dipropyixanthine (hereinafter sometimes referred to as "KW-3902") exhibits an excellent adenosine receptor antagonizing activity, and this compound has been developed as a medicine having an antihypertensive activity, a diuretic activity and kidney-protecting activity (F. Suzuki et al., J. Med. Chem., 35, 3066 (1992)). KW-3902 has attracted attention as a medicine which is especially effective for treating acute renal insufficiency. This KW-3902 is deemed effective in the parenteral administration. KW-3902 is sparingly soluble in water, and it is difficult to produce its preparations. In addition, the compound is problematic in a long-term storage stability. Thus, the development thereof as a medicine has posed a serious problem.

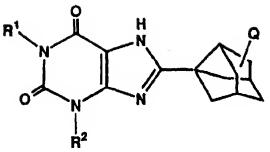
[0004] Meanwhile, a fat emulsion (lipid microsphere) has been already clinically applied for feeding, and also studies to apply the fat emulsion to preparation of an antiinflammatory antalgic agent have been conducted (Mizushima et al., "SAISHIN IGAKU", vol. 40, No. 9, pp. 1806 - 1813, 1985). However, medical ingredients which can be formulated with a fat emulsions are limited, and there have been problems that the stability thereof or the absorption of active ingredients varies depending on the ingredients, the amount, the physical form and the like of the fat emulsion.

Disclosure of the Invention

[0005] The present inventors have conducted studies on production of pharmaceutical preparations of xanthine derivatives, especially 8-(polycycloalkyl)xanthines having excellent long-term storage stability, and have consequently found that pharmaceutical preparations which have high content of sparingly-soluble xanthine derivatives, which exhibit excellent long-term storage stability and which are especially suitable for parenteral administration are obtained through formulation using a fat emulsion.

[0006] The present invention is to provide a stable pharmaceutical preparation of a xanthine derivative or its pharmacologically acceptable salt suitable for parenteral administration. More specifically, the present invention is to provide a pharmaceutical preparation which contains a large amount of a xanthine derivative or its pharmacologically acceptable salt having antihypertensive activity, diuretic activity and kidney-protecting activity, which is especially useful as an agent for preventing, curing or treating renal insufficiency and which has excellent long-term storage stability. That is, the present invention is to provide a stable fat emulsion containing a 8-(polycycloalkyl)xanthine or its pharmacological acceptable salt.

[0007] The present invention relates to a fat emulsion containing a large amount of a xanthine derivative [hereinafter referred to as "Compound (I)"] represented by formula (I)



(I)

wherein R^1 and R^2 are the same or different and each represents a substituted or unsubstituted lower alkyl group, and Q represents hydrogen, a hydroxyl group or a hydroxyl group derivative or its pharmacologically acceptable salt, and having an excellent long-term storage stability.

[0008] In the definition of formula (I), the lower alkyl group includes linear or branched lower alkyl groups having from 1 to 8 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably from 1 to 3 carbon atoms, such as methyl, ethyl, propyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl. Preferable are methyl, ethyl and n-propyl. Examples of the substituent of the substituted lower alkyl group include a hydroxyl, acyl group such as an acetyl group, a carbonyl group (O=) and lower alkoxy group. Of these substituents, a hydroxyl group and an acetyl group are preferable. The lower alkyl group of the lower alkoxy group means the same groups as mentioned above for the lower alkyl group.

[0009] Examples of the hydroxyl group derivative of the substituent Q include an acyloxy group such as an acetoxy group and a lower alkoxy group such as a methoxy group.

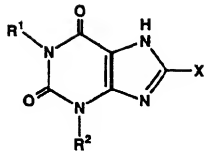
[0010] Examples of the pharmacologically acceptable salt of Compound (I) include an acid addition salt, a metal salt, an ammonium salt, an organic acid amine addition salt and an amino acid addition salt which are pharmacologically acceptable.

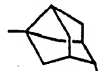
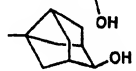
[0011] Examples of the pharmacologically acceptable acid addition salt of Compound (I) include inorganic acid salts such as a hydrochloride, a sulfate and a phosphate; and organic acid salts such as an acetate, a maleate, a fumarate, a tartrate and a citrate. Examples of the pharmacologically acceptable metal salt include alkali metal salts such as a lithium salt, a sodium salt and a potassium salt; alkaline earth metal salts such as a magnesium salt and a calcium salt; an aluminum salt; and a zinc salt. Examples of the pharmacologically acceptable ammonium salt include salts of ammonium and tetramethylammonium. Examples of the pharmacologically acceptable organic amine addition salt include addition salts of morpholine and piperidine. Examples of the pharmacologically acceptable amino acid addition salt include addition salts of lysine, glycine, phenylalanine, glutamic acid and aspartic acid.

[0012] Compound (I) or its pharmacologically acceptable salt can be produced by various methods, for example, by the method described in Japanese Laid-Open (Kokai) No. 173,889/1991.

[0013] Specific examples of Compound (I) are shown in Table 1.

Table 1



Compound Number	R^1	R^2	X
1	n-C_3H_7	n-C_3H_7	
2	n-C_3H_7	n-C_3H_7	
3	n-C_3H_7	n-C_3H_7	
4	CH_3CHCH_2 (OH)	n-C_3H_7	
5	CH_3CCH_2 (O)	n-C_3H_7	

[0014] Compound No. 1 in the above Table 1 is 8-(3-noradamantyl)-1,3-dipropylxanthine (KW-3902).

[0015] The fat emulsion of the present invention contains Compound (I) represented by the formula (I) as an active ingredient, a fatty oil, a surfactant and a pharmaceutically acceptable carrier.

[0016] More specifically, the fat emulsion of the present invention contains the fatty oil in an amount of from 0.5 to 30% (w/v) of fat emulsion, the surfactant in an amount of from 0.1 to 2 times by weight based on the fatty oil, and the pharmaceutically acceptable carrier.

[0017] With respect to the fat emulsion of the present invention, the particle diameter is between 0.005 and 0.3 μm, preferably between 0.02 and 0.15 μm.

[0018] The fat component used in the fat emulsion of the present invention is not particularly limited so long as it is parenterally administrable. Preferable examples thereof include vegetable oils such as soybean oil, sesame oil, olive oil and coconut oil. More preferable is soybean oil.

[0019] With respect to the surfactant to be used in the fat emulsion of the present invention, any surfactant can be used so long as an O/W emulsion can be formed, and the surfactant can be administered parenterally. Preferable examples thereof include egg yoke lecithin, soybean lecithin, highly purified phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidic acid, lysolecithin, polyoxyethylenesorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylated hydrogenated castor oil derivative, polyoxyethylene higher alcohol, and polyoxypropylene polyoxyethylene alkyl ether. More preferable is highly purified phosphatidyl choline.

[0020] With respect to the ratios of the ingredients of the fat emulsion in the present invention, as noted above, the amount of the fat component is between 0.5 and 30% (w/v) based on the total amount of the fat emulsion, and that of the surfactant is between 0.1 and 2 times (weight ratio) of the above-mentioned fat component. An appropriate amount of water is contained in the emulsion.

[0021] The fat emulsion can contain, in addition to the above-mentioned ingredients, an emulsification aid, a stabilizer, an isotonic agent, an antiseptic and the like as required. In the present invention, a fat emulsion containing, besides the fat component and the surfactant, an emulsification aid and an isotonic agent is preferable.

[0022] As the emulsification aid as used in the fat emulsion of the present invention, a saturated or unsaturated fatty acid having from 6 to 22 carbon atoms, preferably from 12 to 20 carbon atoms, or its pharmaceutically acceptable salt is preferable. Examples thereof include lauric acid, myristic acid, palmitic acid, stearic acid and oleic acid. More preferable is oleic acid. The amount of the emulsification aid is 3% (w/v) or less, preferably up to 1% (w/v) based on the total amount of the fat emulsion.

[0023] Examples of the isotonic agent used in the fat emulsion of the present invention include glycerin and dextrose. Preferable is glycerin.

[0024] Preferable examples of the stabilizer used in the fat emulsion of the present invention include cholesterols and phosphatidic acid. The amount thereof is preferably up to 5% (w/v). Preferable examples of the antiseptic used in the fat emulsion of the present invention include benzoic acid and parabens.

[0025] Further, the fat emulsion of the present invention can also be used as a freeze-dried preparation. At this time, an excipient to be used can further be added thereto. Examples of the excipient include mannitol, lactose, maltose, sucrose and inositol.

[0026] The amount of Compound (I) as the active ingredient of the fat emulsion in the present invention can properly be controlled depending on the form of the fat emulsion. Generally, it is between 0.01 μg/ml and 10 mg/ml, preferably between 0.1 μg/ml and 5 mg/ml, more preferably between 0.1 μg/ml and 3 mg/ml of the fat emulsion. It is one of the characteristics of the present invention that sparingly soluble Compound (I) can be contained in a large amount.

[0027] The fat emulsion of the present invention can be produced, for example, by the following method.

[0028] That is, the fat component, the surfactant, Compound (I) and optionally the emulsification aid and the stabilizer in predetermined amounts are mixed, and heated as required to form a solution. The solution is homogenized using an ordinary homogenizer (for example, a homomixer). Subsequently, water containing necessary amounts of the isotonic agent, the stabilizer and the like is added thereto as required, and the mixture is coarsely emulsified using a homogenizer to obtain an oil-in-water emulsion. Then, the resulting suspension is emulsified again by using homogenizer (for example, a high-pressure emulsifier such as MANTON-GAULIN HOMOGENIZER) until a droplet particle diameter becomes between 0.005 and 0.3 μm. From the standpoint of the production, additives such as a stabilizer, an isotonic agent, an antiseptic and the like may be added after the formation of the fat emulsion.

[0029] The product can be purified through dialysis or gel filtration as required.

[0030] The fat emulsion of the present invention can be sterilized and dispensed into an ampoule and then it can be sealed. Further, it can also be freeze-dried as required to form a freeze-dried preparation. The freeze-dried preparation can be used as an emulsion upon using an appropriate solvent when in use.

[0031] The fat emulsion of the present invention can be administered in various manners. Parenteral administration is preferable. The parenteral administration includes intravenous, intramuscular and subcutaneous administrations. The fat emulsion of the present invention is preferably used as an injection. However, it is not critical.

[0032] The present invention provides a pharmaceutically useful fat emulsion which contains a large amount of Compound (I), especially 8-(3-noradamantyl)-1,3-dipropylxanthine and which exhibits an excellent long-term storage stability.

Example

[0033] The present invention is illustrated specifically by referring to the following Examples. However, the present invention is not limited thereto.

[0034] Five-hundred milligrams of KW-3902 (Compound No. 1 in Table 1,; KW-3902 is referred to hereinafter), 50 g

of a soybean oil and 2.4 g of oleic acid were heat-mixed at approximately 60°C. Fifty grams of highly purified phosphatidyl choline, 22.4 g of glycerin and water for injection were added thereto to adjust the total amount to 1,000 ml. The mixture was stirred using a homomixer to form a coarse emulsion. The pH of the coarse emulsion was adjusted to 7, and subjected to emulsification at a high pressure using a microfluidizer to obtain a fine fat emulsion. The emulsion was cooled to room temperature, filtered using a membrane filter having a pore diameter of 0.2 μm, and poured into glass containers. The glass containers were purged with a nitrogen gas, and closed.

Test Example

[0035] The KW-3902-containing fat emulsions prepared in Example were stored at 25°C and 40°C in a thermostat for 30 days, and the residual amount of KW-3902, the discoloration of the fat emulsion and the average particle diameter thereof were measured. The residual amount of KW-3902 was measured through high-performance liquid chromatography under the following conditions. The discoloration was evaluated by diluting to 10 times with isopropyl alcohol and dissolving the fat emulsion and then measuring the absorbance at a wavelength of 455 nm. The average particle diameter was measured using a dynamic light scattering photometer DLS-700 (Otsuka Denshi). The results are shown in Table 2.

High-performance liquid chromatography analysis conditions:

[0036]

Column: Shim-pack CLC-ODS
Mobile phase: acetonitrile: 20 mM potassium dihydrogen phosphate mixed solution (65:35)
Flow rate: 1.0 ml/min
Detection wavelength: Ultraviolet absorption photometer (280 nm)

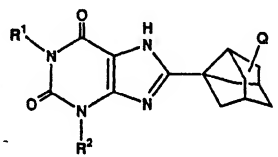
[0037]

Table 2

Stability of a KW-3902-containing fat emulsion			
Sample	Average particle diameter		
	Immediately after formation	25°C - 30 days	40°C - 30 days
Residual ratio of KW-3902	100%	101%	102%
Discoloration	0.001	0.000	0.001
Average particle diameter	0.12 μm	0.11 μm	0.11 μm

Claims

1. A fat emulsion containing a xanthine derivative represented by formula (I)



(I)

wherein R^1 and R^2 are the same or different and each represents
a substituted or unsubstituted lower alkyl group, and Q represents hydrogen, a hydroxyl group or a hydroxyl group derivative
or its pharmacologically acceptable salt.

2. A fat emulsion comprising the xanthine derivative represented by said formula (I), a fatty oil, a sufactant and pharmaceutically acceptable carrier.

3. The fat emulsion claimed in claim 1 or 2, wherein the xanthine derivative represented by said formula (I) is 8-(3-noradamantyl)-1,3-dipropylxanthine.

4. The fat emulsion claimed in claims 1 to 3, wherein the fat is contained in from 0.5% to 30% (w/v) and the surfactant is contained in from 0.1 to 2 times by weight based on said fat.

5. The fat emulsion as claimed in claim 4, wherein the fat is soybean oil, and the surfactant is phosphatidyl choline.

6. The fat emulsion as claimed in any one of claims 1 to 5, wherein the particle diameter is between 0.02 and 0.15 μm.

7. The fat emulsion as claimed in any one of claims 1 to 6, wherein the fat emulsion is a freeze-dried preparation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02773

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl[6] A61K31/52, 9/107, C07D473/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl[6] A61K31/52, 9/107, C07D473/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN), REG(STN), WPIL(QUESTEL)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 5-59056, A (Kyowa Hakko Kogyo Co., Ltd.), March 9, 1993 (09. 03. 93) & EP, 501379, A & US, 5525607, A	1 - 7
A	WO, 94/16702, A (Kyowa Hakko Kogyo Co., Ltd.), August 4, 1994 (04. 08. 94)(Family: none)	1 - 7
A	JP, 63-48223, A (American Cyamanid Co.), February 29, 1988 (29. 02. 88) & EP, 257368, A & DE, 3777721, A	1 - 7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
November 4, 1997 (04. 11. 97)	November 18, 1997 (18. 11. 97)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)